

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE  
 in its capacity as elected Office

|  |  |
|--|--|
| Date of mailing (day/month/year)<br>10 April 2001 (10.04.01)         |  |
| International application No.<br>PCT/US00/12953                      | Applicant's or agent's file reference<br>05118.0002P1    |
| International filing date (day/month/year)<br>12 May 2000 (12.05.00) | Priority date (day/month/year)<br>13 May 1999 (13.05.99) |
| Applicant<br>TOWNES, Tim, M. et al                                   |  |

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
 12 December 2000 (12.12.00)

☐ in a notice effecting later election filed with the International Bureau on:  
 \_\_\_\_\_

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

|   |                                     |
|---|-------------------------------------|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br><br>Anman QIU |
| Facsimile No.: (41-22) 740.14.35  | Telephone No.: (41-22) 338.83.38    |

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

PERRYMAN, David, G.  
Needle & Rosenberg, P.C.  
Suite 1200  
127 Peachtree Street, N.E.  
Atlanta, GA 30303--1811  
ETATS-UNIS D'AMERIQUE

|   |  |
|---|--|
| Date of mailing (day/month/year)<br>21 December 2000 (21.12.00) | <b>IMPORTANT NOTIFICATION</b>  |
| Applicant's or agent's file reference<br>05118.0002P1           |  |
| International application No.<br>PCT/US00/12953                 |  |
|   | International filing date (day/month/year)<br>12 May 2000 (12.05.00) |

|  |  |                      |                    |               |  |               |  |                 |  |
|--|--|----------------------|--------------------|---------------|--|---------------|--|-----------------|--|
| 1. The following indications appeared on record concerning:  |  |                      |                    |               |  |               |  |                 |  |
| <input type="checkbox"/> the applicant   | <input type="checkbox"/> the inventor  |                      |                    |               |  |               |  |                 |  |
| <input checked="" type="checkbox"/> the agent  | <input type="checkbox"/> the common representative   |                      |                    |               |  |               |  |                 |  |
| Name and Address<br>MICHAUD, Susan, M.<br>Clark & Elbing, LLP<br>176 Federal Street<br>Boston, MA 02110-2214<br>United States of America                               | <table border="1"> <tr> <td>State of Nationality</td> <td>State of Residence</td> </tr> <tr> <td colspan="2">Telephone No.</td> </tr> <tr> <td colspan="2">Facsimile No.</td> </tr> <tr> <td colspan="2">Teleprinter No.</td> </tr> </table> | State of Nationality | State of Residence | Telephone No. |  | Facsimile No. |  | Teleprinter No. |  |
| State of Nationality   | State of Residence   |                      |                    |               |  |               |  |                 |  |
| Telephone No.  |  |                      |                    |               |  |               |  |                 |  |
| Facsimile No.  |  |                      |                    |               |  |               |  |                 |  |
| Teleprinter No.  |  |                      |                    |               |  |               |  |                 |  |
| 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:  |  |                      |                    |               |  |               |  |                 |  |
| <input checked="" type="checkbox"/> the person   | <input checked="" type="checkbox"/> the name   |                      |                    |               |  |               |  |                 |  |
| <input checked="" type="checkbox"/> the address  | <input type="checkbox"/> the nationality   |                      |                    |               |  |               |  |                 |  |
| <input type="checkbox"/> the residence   |  |                      |                    |               |  |               |  |                 |  |
| Name and Address<br>PERRYMAN, David, G.<br>Needle & Rosenberg, P.C.<br>Suite 1200<br>127 Peachtree Street, N.E.<br>Atlanta, GA 30303-1811<br>United States of America  | <table border="1"> <tr> <td>State of Nationality</td> <td>State of Residence</td> </tr> <tr> <td colspan="2">Telephone No.</td> </tr> <tr> <td colspan="2">Facsimile No.</td> </tr> <tr> <td colspan="2">Teleprinter No.</td> </tr> </table> | State of Nationality | State of Residence | Telephone No. |  | Facsimile No. |  | Teleprinter No. |  |
| State of Nationality   | State of Residence   |                      |                    |               |  |               |  |                 |  |
| Telephone No.  |  |                      |                    |               |  |               |  |                 |  |
| Facsimile No.  |  |                      |                    |               |  |               |  |                 |  |
| Teleprinter No.  |  |                      |                    |               |  |               |  |                 |  |
| 3. Further observations, if necessary:<br>The person indicated in Box 2 has replaced the person indicated in Box 1 as agent of record for the above noted application. |  |                      |                    |               |  |               |  |                 |  |
| 4. A copy of this notification has been sent to:   |  |                      |                    |               |  |               |  |                 |  |
| <input checked="" type="checkbox"/> the receiving Office   | <input checked="" type="checkbox"/> the designated Offices concerned   |                      |                    |               |  |               |  |                 |  |
| <input type="checkbox"/> the International Searching Authority   | <input type="checkbox"/> the elected Offices concerned   |                      |                    |               |  |               |  |                 |  |
| <input type="checkbox"/> the International Preliminary Examining Authority   | <input type="checkbox"/> other:  |                      |                    |               |  |               |  |                 |  |

|   |   |
|---|---|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br>Facsimile No.: (41-22) 740.14.35 | Authorized officer<br>Anman QIU<br>Telephone No.: (41-22) 338.83.38 |
|---|---|

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: SUSAN MICHAUD  
CLARK & ELBING, LLP  
176 FEDERAL STREET  
BOSTON, MA 02110-2214

## PCT

### NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

|   |  |
|---|--|
| Applicant's or agent's file reference<br>04005/016W02 | Date of Mailing<br>(day/month/year) <b>28 AUG 2000</b>           |
| International application No.<br>PCT/US00/12953       | International filing date<br>(day/month/year) <b>12 MAY 2000</b> |
| Applicant<br>THE UAB RESEARCH FOUNDATION              |  |

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

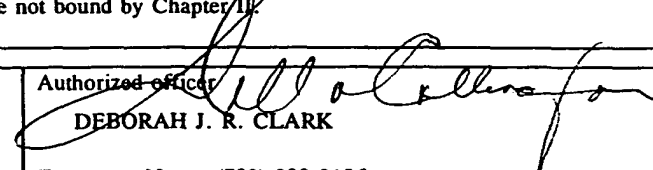
4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau.

If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

|   |   |
|---|---|
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br><br>DEBORAH J. R. CLARK<br>Telephone No. (703) 308-0196 |
|---|---|

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|   |  |
|---|--|
| Applicant's or agent's file reference<br>04005/016W02 | <b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.  |
| International application No.<br>PCT/US00/12953       | <div style="display: flex; justify-content: space-between;"> <div>International filing date (<i>day/month/year</i>)<br/>12 MAY 2000</div> <div>(Earliest) Priority Date (<i>day/month/year</i>)<br/>13 MAY 1999</div> </div> |
| Applicant<br>THE UAB RESEARCH FOUNDATION              |  |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**I. Basis of the report**

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
 

☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
 

☒ the text is approved as submitted by the applicant.  
☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 

☒ the text is approved as submitted by the applicant.  
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is Figure No. \_\_\_\_
 

☐ as suggested by the applicant.  
☐ because the applicant failed to suggest a figure.  
☐ because this figure better characterizes the invention.

☐ None of the figures.

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 16 OCT 2001

WIPO

PCT

|  |   |   |
|--|---|---|
| Applicant's or agent's file reference<br>05118.0002P1  | <b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |   |
| International application No.<br>PCT/US00/12953  | International filing date (day/month/year)<br>12 MAY 2000   | Priority date (day/month/year)<br>13 MAY 1999 |
| International Patent Classification (IPC) or national classification and IPC<br>Please See Supplemental Sheet. |   |   |
| Applicant<br>THE UAB RESEARCH FOUNDATION   |   |   |

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 5 sheets.  
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
These annexes consist of a total of 0 sheets.
- This report contains indications relating to the following items:
  - ☒ Basis of the report
  - ☐ Priority
  - ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
  - ☐ Lack of unity of invention
  - ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
  - ☐ Certain documents cited
  - ☐ Certain defects in the international application
  - ☒ Certain observations on the international application

|  |   |
|--|---|
| Date of submission of the demand<br>12 DECEMBER 2000   | Date of completion of this report<br>27 AUGUST 2001 |
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20531 | Authorized officer<br>PETER BRUNOVSKIS, PH.D.       |
| Facsimile No. (703) 305-3230   | Telephone No. (703) 308-0196                        |

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/12953

## I. Basis of the report

## 1. With regard to the elements of the international application:\*

- ☒ the international application as originally filed  
the description:  
pages 1-9, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_
- ☒ the claims:  
pages 10-14, as originally filed  
pages NONE, as amended (together with any statement) under Article 19  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_
- ☒ the drawings:  
pages NONE, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_
- ☒ the sequence listing part of the description:  
pages NONE, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE  
☒ the claims, Nos. NONE  
☒ the drawings, sheets/fig NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\*

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\*Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/12953

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement

### 1. statement

|                               |                    |     |
|-------------------------------|--------------------|-----|
| Novelty (N)                   | Claims <u>6-19</u> | YES |
|                               | Claims <u>1-5</u>  | NO  |
| Inventive Step (IS)           | Claims <u>6-19</u> | YES |
|                               | Claims <u>1-5</u>  | NO  |
| Industrial Applicability (IA) | Claims <u>1-19</u> | YES |
|                               | Claims <u>NONE</u> | NO  |

### 2. citations and explanations (Rule 70.7)

Claims 1 and 3-5 lack novelty under PCT Article 33(2) as being anticipated by Barker et al.

Barker discloses a thalassemic mouse with a homozygous deletion of the beta-globin allele comprising recipient erythrocytes from another mouse that do not correspond to those naturally occurring in the thalassemic mouse.

Claims 1-4 lack novelty under PCT Article 33(2) as being anticipated by Reisner (US 5,866,757).

Reisner discloses a chimeric mouse or rat with its hematopoietic cells replaced with xenogeneic cells or tissues transplanted from at least two sources: one comprising hematopoietic cells from a mouse with a hematopoietic deficiency, the other comprising xenogeneic cells or tissue from a human (see e.g. col. 4, lines 50-62).

Claims ~~6~~19 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the gene transfer methods or compositions derived from said methods.

NEW CITATIONS

NONE

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention because the description does not provide sufficient guidance teaching how to make and use the breadth of the non-human animals to which the claims are drawn. Specifically, the description lacks sufficient guidance with particularity concerning the specific nature of the cells, tissues, organs, or species, particularly within the context of treatment and fails to provide sufficient guidance, theoretical basis or expectation of success concerning substitution of whole organs or tissues by knocking out one particular gene in a cloning cell to be fused with a reprogramming cell from another organism so as to develop into a blastocyst or embryo into which donor embryonic stem cells can be then introduced so as to result in a chimeric animal in which the cells, tissues or organs from another organism can develop, be stably maintained, and be stably transplantable into a patient in need of a transplant.

The physiological art acknowledged to be unpredictable. This is particularly true in the relatively undeveloped embryonic development art, in which no one has succeeded in producing the types of animals recited in claims 6-19. The process envisioned lacks a great deal of specific guidance and fails to address a number of important challenges, not to mention those directed to the unpredictable nature of development lacking clear and well understood processes that would allow a skilled artisan to reasonably extrapolate the teachings in the art to accommodate the proposed invention. For example, the description does not address the problems of hyperacute rejection or lack of immunologic tolerance. Secondly, the description does not provide sufficient basis or guidance for knocking out specific genes in non-human animals for germ line transfer into animals other than mice. Presently, to produce an animal in which the desired gene has been disrupted, embryonic stem (ES) cells are necessary. Currently, only ES cells for the mouse are available. In particular, no ES cell for animals other than mice exists to date, so the creation of animals which depend on homologous recombination are not enabled in the art. The description lacks specific guidance for making germline knockout animals in species other than mouse and presents no methodology to allow for production of such animals, particularly in the untried and untested process that relies on independent development of non-native organs and tissues within the completely different context of an animal with different signalling properties and developmental requirements than that of the nonnative organs or tissues. Given the unpredictable nature of this highly undeveloped art, and the lack of specific guidance, without an actual reduction to practice, it is impossible to predict whether

(Continued on Supplemental Sheet.)

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/12953

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**CLASSIFICATION:**

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): A01N 63/00; A61K 35/12, 48/00; C12N 15/06, 15/08, 15/09, 15/63; A01K 67/027, 67/033; and US Cl.: 424/93.1, 93.21; 435/449, 455; 800/24, 25, 8, 13, 14, 18;

**VIII. CERTAIN OBSERVATIONS ON THE APPLICATION (Continued):**

any chimeric animal can be produced using the methods of the claimed invention.

Claims 1-19 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to contain an adequate written description commensurate with the claimed subject matter. The description provides for non-human animals wherein the cells, tissues or organs from said animal are replaced with those from a different animal. However, the description fails to describe any specific chimeric animals encompassed by the broad scope of the claimed subject matter with particularity to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the description and which are not conventional in the art at the time of filing. Possession may be shown by actual reduction to practice or by describing the invention with sufficient relevant identifying phenotypic characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. In the instant case, in view of the unpredictability associated the highly undeveloped embryonic development art, the claimed embodiments cannot be adequately described until reduction to practice has occurred, since the skilled artisan cannot envision with any reasonable expectation of success the particular chimeric animals that could possibly be made in accordance with the claimed subject matter.

Claims 1-19 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the immediately preceding paragraph.

Claims 1 and 6-8 (and dependent claims) are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because recitation of the term "corresponding" renders the claims indefinite since it is unclear what the term is directed to, how the term is defined within the context(s) of the claims, or what its metes and bounds are.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/12953

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : Please See Extra Sheet.

US CL : 424/93.1, 93.21; 435/449, 455; 800/24, 25, 8, 13, 14, 18;

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.1, 93.21; 435/449, 455; 800/24, 25, 8, 13, 14, 18;

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category*       | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|-----------------|---|-----------------------|
| X<br>-----<br>Y | BARKER, et al. Hematopoietic Repopulation of Adult Mice With Beta-Thalassemia. Blood. 01 February 1994. Vol. 83. No. 3. Pages 828-832, especially page 828. | 1, 3-5<br>-----<br>2  |
| X               | US 5,866,757 A (REISNER) 02 February 1999, col. 4, lines 53-54, and abstract.   | 1-4                   |
| X               | US 5,876,708 A (SACHS) 02 March 1999, col. 3, lines 50-54.  | 1-4                   |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

|   |  |
|---|--|
| * Special categories of cited documents:  | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  |
| *A* document defining the general state of the art which is not considered to be of particular relevance  | *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone   |
| *E* earlier document published on or after the international filing date  | *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *G* document member of the same patent family  |
| *O* document referring to an oral disclosure, use, exhibition or other means  |  |
| *P* document published prior to the international filing date but later than the priority date claimed  |  |

Date of the actual completion of the international search

02 AUGUST 2000

Date of mailing of the international search report

28 AUG 2000

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

DEBORAH J. R. CLARK

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/12953

**A. CLASSIFICATION OF SUBJECT MATTER:**

IPC (7):

A01N 63/00; A61K 35/12, 48/00; C12N 15/06, 15/08, 15/09, 15/63; A01K 67/027, 67/033;

**B. FIELDS SEARCHED**

Electronic data bases consulted (Name of data base and where practicable terms used):

USPAT, MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, CABA, WPIDS

search terms: cell, replace, delete, defect, knockout, substitute, deficient, xenogeneic, endogenous, gata-2, lmo-2, globin, erythropoietin receptor, pdx-1, insulin promoter factor-1

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

**What parts of the international application may be amended ?**

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

**When ?** Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

**Where not to file the amendments ?**

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

**How ?** Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

**What documents must/may accompany the amendments ?**

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|  |           |  |
|--|-----------|--|
| <p>(51) International Patent Classification <sup>7</sup> :<br/>A01N 63/00, A61K 35/12, 48/00, C12N 15/06, 15/08, 15/09, 15/63, A01K 67/027, 67/033</p>   | <p>A1</p> | <p>(11) International Publication Number: <b>WO 00/69268</b><br/>(43) International Publication Date: 23 November 2000 (23.11.00)</p>  |
| <p>(21) International Application Number: PCT/US00/12953<br/>(22) International Filing Date: 12 May 2000 (12.05.00)<br/>(30) Priority Data:<br/>60/133,935 13 May 1999 (13.05.99) US<br/>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application<br/>US 60/133,935 (CIP)<br/>Filed on 13 May 1999 (13.05.99)<br/>(71) Applicant (for all designated States except US): THE UAB RESEARCH FOUNDATION [US/US]; University of Alabama at Birmingham, 1825 University Boulevard, Mortimer Jordan Hall #113, Birmingham, AL 35294 (US).<br/>(72) Inventors; and<br/>(75) Inventors/Applicants (for US only): TOWNES, Tim, M. [US/US]; 4687 Bridgewater Road, Birmingham, AL 35243 (US). RYAN, Thomas [US/US]; 1610 Cahaba Road, Birmingham, AL 35223 (US).</p> |           | <p>(74) Agent: MICHAUD, Susan, M.; Clark &amp; Elbing, LLP, 176 Federal Street, Boston, MA 02110-2214 (US).<br/>(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b><br/>With international search report.</p> |
| <p>(54) Title: PRODUCTION OF HUMAN CELLS, TISSUES, AND ORGANS IN ANIMALS<br/>(57) Abstract<br/><br/>The invention provides animals that produce cells, tissues, and organs of another organism; methods of generating such animals; cells, tissues, and organs produced by such methods; and methods of using such cells, tissues, and organs to treat disease.</p>  |           |  |

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

|    |                          |    |  |    |  |    |                          |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania                  | ES | Spain                                    | LS | Lesotho                                      | SI | Slovenia                 |
| AM | Armenia                  | FI | Finland                                  | LT | Lithuania                                    | SK | Slovakia                 |
| AT | Austria                  | FR | France                                   | LU | Luxembourg                                   | SN | Senegal                  |
| AU | Australia                | GA | Gabon                                    | LV | Latvia                                       | SZ | Swaziland                |
| AZ | Azerbaijan               | GB | United Kingdom                           | MC | Monaco                                       | TD | Chad                     |
| BA | Bosnia and Herzegovina   | GE | Georgia                                  | MD | Republic of Moldova                          | TG | Togo                     |
| BB | Barbados                 | GH | Ghana                                    | MG | Madagascar                                   | TJ | Tajikistan               |
| BE | Belgium                  | GN | Guinea                                   | MK | The former Yugoslav<br>Republic of Macedonia | TM | Turkmenistan             |
| BF | Burkina Faso             | GR | Greece                                   |    |  | TR | Turkey                   |
| BG | Bulgaria                 | HU | Hungary                                  | ML | Mali   | TT | Trinidad and Tobago      |
| BJ | Benin                    | IE | Ireland                                  | MN | Mongolia                                     | UA | Ukraine                  |
| BR | Brazil                   | IL | Israel                                   | MR | Mauritania                                   | UG | Uganda                   |
| BY | Belarus                  | IS | Iceland                                  | MW | Malawi                                       | US | United States of America |
| CA | Canada                   | IT | Italy                                    | MX | Mexico                                       | UZ | Uzbekistan               |
| CF | Central African Republic | JP | Japan                                    | NE | Niger  | VN | Viet Nam                 |
| CG | Congo                    | KE | Kenya                                    | NL | Netherlands                                  | YU | Yugoslavia               |
| CH | Switzerland              | KG | Kyrgyzstan                               | NO | Norway                                       | ZW | Zimbabwe                 |
| CI | Côte d'Ivoire            | KP | Democratic People's<br>Republic of Korea | NZ | New Zealand                                  |    |                          |
| CM | Cameroon                 |    |  | PL | Poland                                       |    |                          |
| CN | China                    | KR | Republic of Korea                        | PT | Portugal                                     |    |                          |
| CU | Cuba                     | KZ | Kazakstan                                | RO | Romania                                      |    |                          |
| CZ | Czech Republic           | LC | Saint Lucia                              | RU | Russian Federation                           |    |                          |
| DE | Germany                  | LI | Liechtenstein                            | SD | Sudan  |    |                          |
| DK | Denmark                  | LK | Sri Lanka                                | SE | Sweden                                       |    |                          |
| EE | Estonia                  | LR | Liberia                                  | SG | Singapore                                    |    |                          |

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

**RECEIVED**

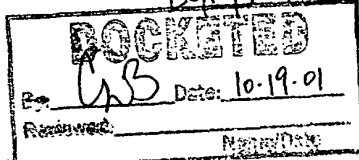
**PCT**

To: DAVID G. PERRYMAN  
NEEDLE & ROSENBERG, P.C.  
127 PEACHTREE STREET, N.E.  
SUITE 1200  
ATLANTA, GA 30303 1811

OCT 19 2001

**NOTIFICATION OF TRANSMITTAL OF  
INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

(PCT Rule 71.1)



Date of Mailing  
(day/month/year)

12 OCT 2001

Applicant's or agent's file reference

05118.0002P1

**IMPORTANT NOTIFICATION**

International application No.

PCT/US00/12953

International filing date (day/month/year)

12 MAY 2000

Priority Date (day/month/year)

13 MAY 1999

Applicant

THE UAB RESEARCH FOUNDATION

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

PETER BRUNOVSKIS, PH.D.

Telephone No. (703) 305-0196